



Published in final edited form as:

Obstet Gynecol. 2015 November ; 126(5): 1069–1074. doi:10.1097/AOG.0000000000001066.

Safety of Tetanus, Diphtheria, and Acellular Pertussis and Influenza Vaccinations in Pregnancy

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Abstract

Objective—To evaluate the safety of co-administering tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) and influenza vaccines during pregnancy by comparing adverse events after concomitant and sequential vaccination.

Methods—We conducted a retrospective cohort study of pregnant women aged 14–49 years in the Vaccine Safety Datalink from January 1, 2007 to November 15, 2013. We compared medically attended acute events (fever, any acute reaction) and adverse birth outcomes (preterm delivery, low birth weight, small for gestational age) in women receiving concomitant Tdap and influenza vaccination and women receiving sequential vaccination.

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The other authors did not report any potential conflicts of interest.

Results—Among 36,844 pregnancies in which Tdap and influenza vaccines were administered, the vaccines were administered concomitantly in 8,464 (23%) pregnancies, and sequentially in 28,380 (77%) pregnancies. Acute adverse events after vaccination were rare. We found no statistically significant increased risk of fever or any medically attended acute adverse event in pregnant women vaccinated concomitantly compared to sequentially. When analyzing women at 20 weeks of gestation or greater during periods of influenza vaccine administration, there were no differences in preterm delivery, low birth weight or small-for-gestational-age infants between women vaccinated concomitantly compared with sequentially in pregnancy.

Conclusion—Concomitant administration of Tdap and influenza vaccines during pregnancy was not associated with a higher risk of medically attended adverse acute outcomes or birth outcomes compared to sequential vaccination.

Introduction

Inactivated influenza vaccine is recommended at any time during pregnancy to protect pregnant women and their infants from the complications of influenza infection (1), and more recently, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine has been recommended during pregnancy, with a preference for administration between 27–36 weeks of gestation to maximize maternal antibody response and transfer to the infant (2). The safety and benefits of influenza vaccination during pregnancy have been well studied (3–6). Vaccination during pregnancy decreases morbidity in the pregnant women and also protects the infants from disease caused by influenza infection. Recently, a few studies have shown that the Tdap vaccine is safe in pregnancy (7–10), and others have shown effectiveness in decreasing the burden of pertussis in infants (11, 12).

Studies evaluating the safety of co-administering Tdap and influenza vaccines in non-pregnant individuals have not found an increased risk of adverse events when compared to sequential vaccination (13, 14). Given the likelihood that concomitant vaccination will occur in pregnancies that overlap with the influenza season, and the potential for different responses to vaccinations in pregnant women compared to non-pregnant individuals (15), we evaluated whether there was an increased risk of medically attended acute events or adverse birth outcomes when Tdap and influenza vaccines are administered concomitantly during pregnancy.

Materials and Methods

We conducted a retrospective cohort study using data from the Vaccine Safety Datalink to assess the safety of concomitant Tdap and influenza vaccine administration in pregnancies ending in live births by evaluating medically attended acute events and adverse birth outcomes in women who received Tdap and influenza vaccines on the same day compared to different days (sequentially) in pregnancy.

The Vaccine Safety Datalink is a collaborative project between the Centers for Disease Control and Prevention (CDC) and 9 integrated health care organizations with an annual birth cohort of approximately 90,000 per year (16). For this study, seven Vaccine Safety Datalink sites contributed data: Group Health Cooperative (WA), Kaiser Permanente

Northwest (OR) and (WA), Kaiser Permanente Northern California (CA), Southern California Kaiser Permanente (CA), HealthPartners (MN), Marshfield Clinic (WI), and Kaiser Permanente Colorado (CO).

We identified pregnancies ending in live births between January 1, 2007 and November 15, 2013 using a validated algorithm (17) used in prior Vaccine Safety Datalink pregnancy studies (3, 4). This pregnancy episode algorithm uses claims, administrative, and birth data to identify pregnancies and their associated outcomes and dates.

We included pregnant women aged 14–49 years who received Tdap and influenza vaccines during pregnancy and had continuous insurance coverage from 6 months prior to pregnancy to 6 weeks postpartum with no greater than a 30 day gap in enrollment. We excluded women who received any live vaccines in pregnancy, those with multiple gestations, and those with non-live birth outcomes, including stillborn, spontaneous abortion, therapeutic abortion, trophoblastic disease, and ectopic pregnancy, since we did not access medical records to confirm these outcomes and their onset dates. Additionally, we excluded women who received more than one tetanus containing vaccine (including multiple Tdap vaccines) in the same pregnancy and women who received more than one influenza vaccine (seasonal influenza and H1N1 influenza or multiple seasonal influenza vaccines) on different days in the same pregnancy, in order to limit our comparisons to women with a single influenza vaccination date and a single tetanus vaccination date. For example, a woman who received a seasonal influenza vaccine and an H1N1 influenza vaccine on the same day would be included in the cohort, but if she received these vaccines on different days, she would be excluded. Women may have received multiple vaccinations of the same strain during pregnancy in cases where a pregnancy spanned two different influenza vaccination seasons (i.e. February and September of same calendar year) or in cases of provider error.

We identified Tdap and influenza vaccinations administered during pregnancy using electronic medical record and claims data. We defined a vaccine administered during pregnancy as one given from 7 days after the last menstrual period through 7 days before the pregnancy end date. We used these cut offs to avoid inadvertently including vaccines that might have been given prior to pregnancy or in the post-partum period (18).

We compared baseline characteristics between the two cohorts using chi-squared tests for categorical variables and t-test for continuous variables. We used a log binomial regression analysis in order to calculate the relative risks for both rare (acute outcomes) and non-rare (birth outcomes) events. We identified all covariates and medically attended acute events using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes. We adjusted for differences in Vaccine Safety Datalink site and gestational age at Tdap vaccination as a linear covariate when comparing acute events. Additionally, we adjusted for maternal age, the presence of a maternal comorbidity (from 6 months prior to pregnancy through 30 days postpartum), the presence of a pregnancy complication, season of delivery, prenatal care utilization (19), and length of enrollment prior to pregnancy when comparing birth outcomes. We tested for effect modification by gestational age in weeks at Tdap vaccination for each outcome. All analyses were performed using Statistical Analysis System (SAS) software, version 9.3 (Cary, North Carolina).

We compared medically attended acute outcomes (fever, limb pain, limb swelling, cellulitis, lymphadenitis, Arthus reaction, allergy, urticaria, and anaphylaxis) between concomitant and sequential vaccine recipients in the 0–3 and 0–7 days after Tdap and influenza vaccines. Outpatient diagnosis codes on the day of vaccination were excluded, as the diagnosis was likely present before the vaccination. We also compared the risk of incident Guillain-Barré syndrome occurring 1–42 days after vaccination. The day of vaccination was considered day 0. For the group of concomitant vaccine recipients, we examined events in three risk windows after vaccination (0–3, 0–7, and 1–42 days). For the group of sequentially vaccinated women, we examined each of the three windows after both Tdap and influenza vaccination dates. The time windows were allowed to overlap in women receiving vaccinations on separate days.

We compared the following birth outcomes between the groups: preterm delivery (defined as gestational age <37 weeks), low birth weight (LBW, birth weight <2500 grams), and small for gestational age (SGA, <10th percentile for gestational age and sex) (20). We had initially planned to perform the analysis on the entire cohort; however, based on further evaluation examining the seasonal differences in influenza vaccine administration and differences in the gestational age at which Tdap vaccine is preferentially administered, we limited our analysis of adverse birth outcomes to women vaccinated during periods of peak influenza vaccine administration (September through January) and vaccinated at 20 weeks of gestation or greater. This allowed us to capture women who had an opportunity to be in either cohort, since they would be eligible for concomitant or sequential vaccination. Additionally, this would address biases associated with the seasonal differences in birth outcomes (21). Finally, we limited our analysis of birth outcomes to women vaccinated prior to 37 weeks of gestation, so as to not bias our results towards any protective effect of vaccination (22, 23) and to pregnancies with known gestational age and birth weight recorded in the electronic health record or linked to the state birth registries.

We performed *a priori* power calculations and determined that we had 80% or higher power to detect relative risks of greater than 2 for all of our birth outcomes, even with the restricted cohort. However, our analyses for medically attended acute outcomes, which are rare, were underpowered. For this reason, we limited our analysis of acute outcomes to fever and any acute event (37,000 and 10,000 pregnancies needed in each cohort respectively to detect a relative risk of 2). We considered results to be statistically significant at an alpha error less than 0.05 using 2-tailed tests. The study protocol was reviewed and approved by Institutional Review Boards at Emory University, CDC, and the 7 Vaccine Safety Datalink sites.

Results

During our study period, we identified 633,542 total singleton pregnancies, 443,774 of which ended in live births Figure 1). Our final analytic cohorts for the analysis of acute events consisted of 8,464 (23%) pregnancies with concomitant Tdap and influenza vaccine administration and 28,380 (77%) pregnancies with sequential Tdap and influenza vaccine administration. When comparing baseline characteristics, the cohorts were similar in maternal age, enrollment in the health care plan prior to pregnancy, prenatal care utilization,

comorbidities, and the receipt of other vaccinations during pregnancy. Most comparisons were statistically significantly different, but not necessarily clinically relevant, with the exception of gestational age at Tdap and influenza vaccination, which was 25 weeks (range 1–40 weeks) in the women vaccinated on the same day in pregnancy and 27 weeks (range 1–41 weeks) for Tdap vaccine and 19 weeks (range 1–40 weeks) for influenza vaccine for women vaccinated on different days ($p < 0.001$). Of women vaccinated on different days during pregnancy, the mean number of days between Tdap and influenza vaccines was 94 days with a median of 84 days. The study cohort size for birth outcomes was 4,554 (51%) pregnancies with concomitant Tdap and influenza vaccine administration and 4,440 (49%) with sequential Tdap and influenza vaccine administration. Distribution of baseline characteristics were similar to the full cohort (data not shown).

For the entire cohort of 36,844 vaccinated women, Tdap vaccine was most often administered later in pregnancy (37% in second trimester, 56% in third trimester), while influenza vaccine was administered relatively evenly throughout pregnancy (34% given in the first trimester, 34% in the second trimester, 32% in the third trimester). Women vaccinated with Tdap and influenza vaccines on different days received influenza vaccine earlier in pregnancy, and Tdap vaccine later in pregnancy than women vaccinated on the same day in pregnancy. The peak birth year was 2011 for women vaccinated with Tdap and influenza vaccines on the same day (36%) and 2013 for women vaccinated on different days (44%), likely representing changes to the ACIP recommendations made emphasizing timing of Tdap vaccination after 2012. Very few vaccinations occurred in the years 2007–2009 (<2% of cohort), when Tdap was not routinely recommended during pregnancy.

There were no differences between women receiving Tdap and influenza vaccines concomitantly compared to sequentially for medically attended fever and any acute event within three and seven days after vaccination (Table 1). Overall, acute adverse events after vaccination were rare. There were no cases of Arthus reaction or Guillain Barré Syndrome after vaccination. There was no interaction between acute adverse events and gestational age at Tdap vaccination (data not shown).

In women who were vaccinated after 20 weeks of gestation during the period of peak influenza vaccination administration, there were no differences in the occurrence of preterm delivery, LBW, and SGA infants for women receiving concomitant Tdap and influenza vaccines compared to women vaccinated sequentially (Table 2). There was no interaction between adverse birth outcomes and gestational age at time of Tdap vaccination (data not shown). As a post-hoc descriptive analysis of the cohort used to evaluate birth outcomes, we found that, as expected, most deliveries were occurring in the winter months in both concomitantly and sequentially vaccinated women.

Discussion

In our study of pregnant women receiving Tdap and influenza vaccines, we found no significant differences in the risk of medically attended acute outcomes between concomitant and sequential vaccination. Moreover, we found no differences in preterm

delivery, LBW or SGA infants when Tdap and influenza vaccines were co-administered at 20 weeks of gestation or later during peak influenza vaccine administration.

Our results are similar to randomized studies that have shown no difference in acute events after concomitant and sequential Tdap and influenza vaccination in non-pregnant individuals (13, 14).. Both prior studies solicited adverse events from patients, while our study relied on diagnosis codes from medical visits.

Our study is similar to a Vaccine Safety Datalink study evaluating adverse obstetrical events and birth outcomes after Tdap vaccine in pregnancy (10), which included a cohort of pregnant women that overlapped with the women evaluated in our study. There are a few differences between the two studies. First, the prior study compared Tdap vaccinated women to a cohort of unvaccinated women, while we compared two vaccinated cohorts receiving both Tdap and influenza vaccine. Additionally, that study adjusted for the exposure to influenza vaccine, while all of our women were exposed. Finally, the prior study used a time dependent Cox model to evaluate preterm delivery, while we used a log binomial model to evaluate preterm delivery. Despite these differences, both studies have similar results, which provides additional reassurance of the safety of Tdap and influenza vaccine in pregnancy.

One limitation to our study is that we analyzed only acute events in women who sought medical care. However, since pregnant women have frequent medical encounters, especially later in pregnancy, minor events may be more likely to be diagnosed and coded in pregnant women. The rarity of adverse events in our cohort may also be related to differences in the immune response that occur during pregnancy in order to protect the fetus (15). Such differences may result in pregnant women being less reactogenic in response to vaccines.

Another limitation is that we did not use chart review to determine if an adverse outcome was related to vaccination. However, this non-differential misclassification bias should not affect our overall results. We also had two risk windows for women receiving sequential vaccination compared to one risk window for women receiving concomitant vaccination, which could have made the risk appear higher in the sequentially vaccinated women, however, this was not the case. We relied on birth weight and gestational age data from the electronic medical record and birth certificates. We believe them to be accurate based on prior validation work which has shown a positive predictive value of greater than 90% between birth certificate and medical record data at the research sites included in this study (24). We were unable to adjust for all potential confounders, including race and ethnicity, smoking status, and prior preterm delivery. Finally, we did include long term follow up of the infants to monitor for any adverse events.

We observed there are both seasonal differences in influenza vaccine administration and differences in the gestational age at which Tdap vaccine is administered in pregnancy. In our cohort, influenza vaccine was primarily given during the months of September through January, and was administered evenly throughout pregnancy. On the other hand, while Tdap vaccine can be given during any stage of pregnancy, the ACIP gives preference to vaccination later in pregnancy. In our cohort, Tdap vaccine was generally administered during the second and third trimesters. Because of the combination of limited months of

influenza vaccine administration and Tdap vaccine administration later in pregnancy, not all women were eligible for concomitant vaccination. For this reason, we limited our analysis of adverse birth outcomes to women vaccinated at 20 weeks of gestation or later during the months of September to January. This was important in order to avoid confounding related to seasonality of birth outcomes. Future studies are needed to evaluate non-live birth outcomes, such as stillbirth and spontaneous abortions.

We found no differences in medically attended acute events or adverse birth outcomes in pregnant women receiving concomitant or sequential vaccination with Tdap and influenza vaccines. Our findings should be reassuring to providers and pregnant women, especially for women who are later in their pregnancy during months of influenza vaccine administration and are most likely to receive concomitant vaccination.

Acknowledgments

The authors thank Robert A. Bednarczyk and Paige W. Lewis for their assistance with the statistical analysis.

Financial Disclosure: Dr. Sukumaran has received research support from award number T32AI074492 from the National Institute of Allergy and Infectious Diseases. Dr. Klein has received research support from GlaxoSmithKline, Sanofi Pasteur, Merck & Co, Pfizer, Nuron Biotech, MedImmune, Novartis, and Protein Science. Dr. Naleway has received research support from GlaxoSmithKline and Pfizer.

The Vaccine Safety Datalink Project is funded by the Centers for Disease Control and Prevention.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the Centers for Disease Control and Prevention, the National Institute of Allergy and Infectious Diseases or the National Institutes of Health.

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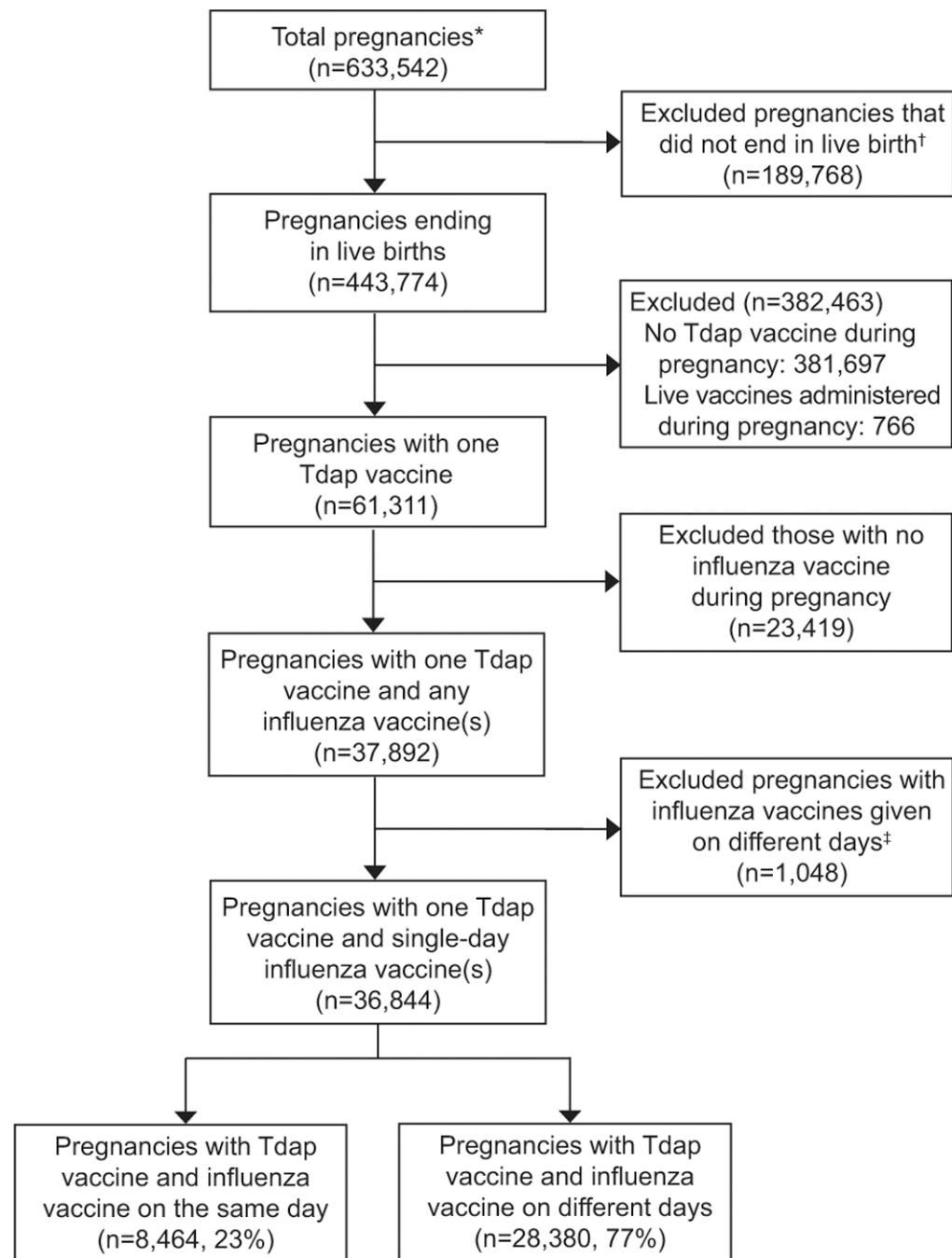


Figure 1.

Pregnant women in the Vaccine Safety Datalink vaccinated with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) and influenza vaccines in pregnancy: 2007–2013. *Singleton pregnancies. †Non-live birth includes stillborn, spontaneous abortion, therapeutic abortion, trophoblastic disease, ectopic pregnancy, and unknown outcomes. ‡Women were given either two seasonal influenza vaccinations or a seasonal influenza and H1N1 influenza vaccination on different days in pregnancy.

Table 1

Medically attended acute outcomes after Tdap and influenza vaccinations in pregnancy

Outcome	Concomitant Tdap + influenza (N = 8,464)	Sequential Tdap + influenza (N = 28,380) *	Unadjusted risk difference (95% CI)	Unadjusted relative risk (95% CI)	Adjusted [†] relative risk (95% CI)	P-value
Fever (0-3 days)	2 (2.4)	9 (3.2)	-1 (-5, 3)	0.75 (0.16 - 3.45)	0.69 (0.15 - 3.23)	0.64
Fever (0-7 days)	3 (3.5)	12 (4.2)	-1 (-5, 4)	0.84 (0.24 - 2.97)	1.60 (0.56 - 4.59)	0.38
Any acute reaction (0-3 days)	11 (13.0)	32 (11.3)	2 (-7, 10)	1.15 (0.58 - 2.29)	1.13 (0.57 - 2.27)	0.72
Any acute reaction (0-7 days)	19 (22.4)	72 (25.4)	-3 (-15, 9)	0.88 (0.53 - 1.47)	0.96 (0.58 - 1.61)	0.88

Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

* N (rate/10,000)

[†] Adjusting for gestational age at Tdap vaccination in weeks and Vaccine Safety Datalink site.

Table 2

Birth outcomes for same day Compared With different day vaccination with Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis and Influenza in pregnancy

Outcome	Concomitant Tdap + influenza (N = 4,554)	Sequential Tdap + influenza (N = 4,440)	Unadjusted risk difference (95% CI)	Unadjusted relative risk (95% CI)	Adjusted* relative risk (95% CI)	P-value
Preterm delivery	333 (7.3%)	295 (6.6%)	0.7 (-0.4, 1.7)	1.10 (0.95 – 1.28)	0.95 (0.82 – 1.11)	0.52
Low birth weight	266 (5.8%)	252 (5.7%)	0.2 (-0.8, 1.1)	1.03 (0.87 – 1.22)	0.92 (0.78 – 1.09)	0.34
Small for gestational age	439 (9.6%)	432 (9.7%)	-0.1 (-1.3, 1.1)	0.99 (0.87 – 1.12)	1.01 (0.88 – 1.15)	0.92

Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

* Adjusting for gestational age at Tdap vaccination in weeks, Vaccine Safety Datalink site, length of enrollment (months), prenatal care utilization index, maternal comorbidity, pregnancy complication, maternal age, seasonality of preterm delivery